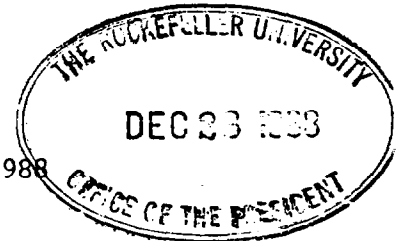


**WASHINGTON
UNIVERSITY
SCHOOL OF
MEDICINE**
AT WASHINGTON UNIVERSITY MEDICAL CENTER

DEPARTMENT OF
GENETICS

Daniel L. Hartl
McDonnell Professor and Head

December 21, 1988



Dr. Joshua Lederberg
The Rockefeller University
1230 York Avenue
New York, New York 10021-6339

Dear Josh:

It is good to know you still have time to read in evolutionary biology in spite of your heavy administrative duties.

Enclosed is the paper with Tony Dean you requested. The experimental material consists of amino acid replacements in the lacZ β -galactosidase obtained as spontaneous revertants of nonsense codons that restored enzyme synthesis but altered its electrophoretic mobility or thermostability as compared with wildtype. The result was unexpected in that most of the amino acid replacements produced effects too small to be detected in chemostat competition experiments with the parental wildtype strain. Among 25 amino acid replacements in β -galactosidase obtained in 17 codons distributed approximately uniformly along the gene, only three produced selective effects large enough to be significant in chemostats. The remaining 22 produced effects that could not be detected under conditions in which the limit of resolution was a selection coefficient of approximately 0.4 percent per generation. I suspect that many of the amino acid replacements actually resulted in small differences in enzyme activity, but that these gave undetectable effects in chemostats owing to the small control coefficient of β -galactosidase with respect to fitness.

Best regards for the holiday season and best wishes for a healthy and happy New Year.

Thank you, Dan.

My interest in this title has to do with the "cost of evolution", leading back to a paper by Kimura many years ago. It is now obvious that there are far less than 6×10^9 bits of information in the human genome — which has some bearing on cost-effective strategies for understanding it.

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*I assume you are running
chemostats under carbon (glucose)
limitation. This will stress just one
aspect of permissiveness/leakage function —
avidity for
very low
concentration*

*Doesn't period
selection (drift)
interfere with
precise measure
ment of
selective
advantage
of*

Sincerely,

Daniel L. Hartl
McDonnell Professor and
Head, Department of Genetics

Young J.